Actas de Investigación Oncológica

Artículo Original

Hypothesis: allogeneic bone marrow transplantation as possible immunotherapy in solid tumors

Kevin Doello 1, Cristina Mesas 2,3

1 Medical Oncology Service, Virgen de las Nieves Hospital, Granada, Spain
2 Institute of Biopathology and Regenerative Medicine (IBIMER), Center of Biomedical Research (CIBM), University of Granada, Granada, Spain
3 Department of Anatomy and Embryology, University of Granada, Granada, Spain

*Corresponding author: Kevin Doello, kdoello@correo.ugr.es

Abstract

Bone marrow transplantation has been used as experimental therapy in solid tumors, but favorable results have been achieved only in lymphomas and germinal tumors. Recent investigations have reported MHC-I haplotype loss in cancer cells in approximately 30% of solid tumors. Based on these findings, we hypothesize that allogenic bone marrow haploidentical transplantation would induce a graft-versus-tumor reaction, and thus it could be an effective treatment for cancer.

Keywords: Cancer, allogeneic bone marrow transplantation, graft-versus-tumor reaction, MHC-I.

Introduction

Traditionally, bone marrow transplantation has been used in the treatment of hematological malignancies (leukemias), allowing patients to receive myeloablative doses of chemotherapy and to take advantage of the graft-versus-tumor effect.[1] In Medical Oncology practice, bone marrow transplantation has been also contemplated as a means to provide high-dose chemotherapy in lymphomas and germinal tumors.[2] Likewise, bone marrow transplantation has been tried in solid tumors such as breast cancer to increase tolerance to higher doses of chemotherapy. However, no significant improvement in terms of treatment effectiveness has been demonstrated.[3] In sum, although bone marrow transplantation has been traditionally used to increase chemotherapy tolerance and/or the efficacy of conventional therapies, it has never been used to induce a cellular rejection response against tumor tissues.

Hypothesis

Our hypothesis consists of using allogeneic transplantation of hematopoietic precursors as a therapeutic weapon against solid tumors based on a graft-versus-tumor reaction. Because loss of Major Histocompatibility Complex type 1 (MHC-I) haplotype has been reported in more than 30% of solid tumors[4], using a bone marrow MHC-haplotype compatible with that loss would generate a graft-versus-tumor reaction. By contrast, the transplanted bone marrow would show tolerance towards healthy tissues since they would share the same MHC-I haplotype. Therefore, it would be necessary to select a bone marrow with the same haplotype for MHC-I (i.e. HLA-A, HLA-B or HLA-C) as the haplotype lost in the tumor cells. Newly generated T lymphocytes by the patient would share one MHC-I

haplotype with the receptor, so there would be no rejection against non-tumor cells. However, these T lymphocytes would induce an intense immunological response against tumor cells. Moreover, Natural Killer (NK)-dependent cell killing mechanisms would be activated given the presence of an MHC-I molecule not recognizable by the immune system.[5, 6] Figure 1 (see below) summarizes the immunological mechanisms stated in our hypothesis. It must be stressed that this kind of transplantation would be haploidentical, which implies the need for a special processing of bone marrow precursors in order to minimize the risk of rejection against healthy tissues.[7]

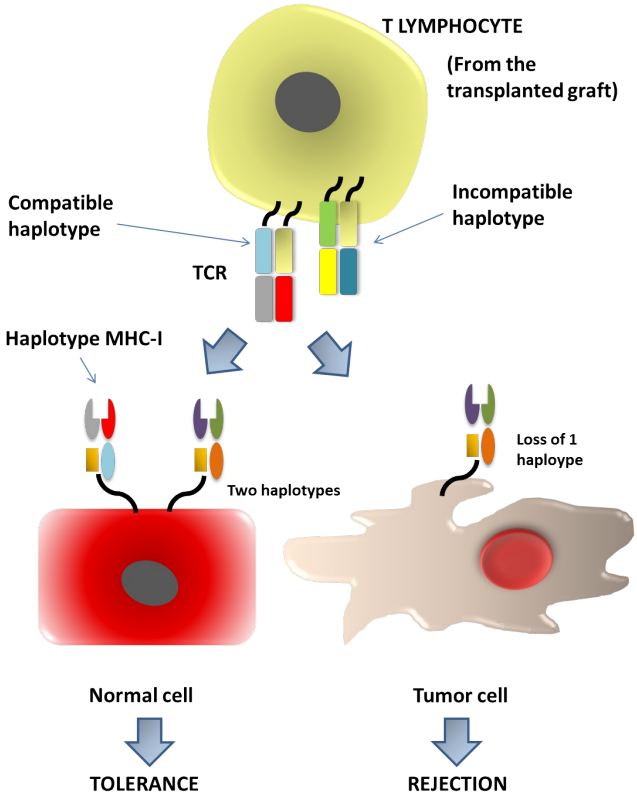

Figure 1. Immunological mechanisms underlying our hypothesis. T lymphocytes from the transplanted graft would be compatible only with one of the two haplotypes of the receptor (haploidentical transplantation). Such compatibility would prevent healthy tissues from destruction by T cells. Conversely, tumor cells that lost the compatible haplotype would be recognized as foreign cells by transplanted T lymphocytes and destroyed by T cells and NK cells.

Supporting arguments

Recently, immune-checkpoints such as PD-1, PDL-1, PDL-2 or CTLA-4 have been discovered. These checkpoints play a major role in the escape of tumor cells from immune surveillance and have served as molecular targets for antibody-based therapies with monoclonal antibodies such as nivolumab, ipilimumab or atezolizumab[8] A few years ago, research on mechanisms of tumor escape from immune surveillance focused on the modulation of MHC-I expression by tumor cells. After many analyses of MHC-I expression, six phenotypes were established: i) MHC-I expression without modulation (23-26%), ii) total loss of MHC-I expression (phenotype 1) (11-25%), iii) loss of an MHC-I haplotype (phenotype 2) (19-34%), iv) loss of an MHC-I locus (phenotype 3) (6-16%); v) MHC-I allelic loss (phenotype 4) (10-15%), and vi) mixed phenotype (10-15%).

Haplotype loss has been specially described in tumors of the prostate[9], larynx[10], colon[11], melanoma[12], pancreas[13], and non-Hodgkin's lymphoma.[14] It has also been described in non-microcytic lung cancer in up to 42% of the cases studied.[15] MHC-I haplotype loss can be detected in approximately 30% of solid tumors, and it is usually due to the loss of one of the two copies of chromosome 6 or its fragments (p arm) during oncogenesis.[4] Therefore, an immune response could be targeted against these tumors using an allogeneic bone marrow transplantation only compatible with the lost haplotype. This would lead to tumor rejection along with healthy tissue tolerance.

Currently, therapies known as CAR and TCR are being developed. Briefly, they consist of designing T cells with TCR receptors with different degrees of chimerism aimed to recognize tumor-associated antigens. However, despite their favorable results, neurological toxicity based on the similarity between tumor and healthy tissue antigens[16] is a major therapeutic limitation. The treatment proposed herein

would avoid such inconvenient, ensuring compatibility with healthy tissues.

Conclusions

MHC-I haplotype loss observed in a high percentage of solid tumors (19-34%) may provide a basis for the design of new therapies. Allogeneic bone marrow haploidentical transplantation sharing the haplotype lost in tumor cells could be used as a therapeutic strategy in tumors with this molecular anomaly, especially in patients who have exhausted all treatment options and present good Performance Status.

References

1. Campbell T. Hematology. New York, NY: Elsevier 2015.

2. DeVita V, Lawrence T, Rosenberg S. Cancer. Philadelphia: Wolters Kluwer Health 2015.

3. Rettig R. False Hope: Bone Marrow Transplantation for Breast Cancer. Oxford University Press 2007.

4. Aptsiauri N, Garcia-Lora A, Cabrera T. MHC class I antigens in malignant cells. New York, NY: Springer 2013.

5. Ingulli E. Mechanism of cellular rejection in transplantation. Pediatric Nephrology 2008;25:61-74.

6. Benichou G, Yamada Y, Aoyama A, Madsen J. Natural killer cells in rejection and tolerance of solid organ allografts. Current Opinion in Organ Transplantation 2011;16:47-53.

7. Luznik L, O'Donnell P, Symons H, Chen A, Leffell M, Zahurak M et al. HLA-Haploidentical Bone Marrow Transplantation for Hematologic Malignancies Using Nonmyeloablative Conditioning and High-Dose, Posttransplantation Cyclophosphamide. Biology of Blood and Marrow Transplantation 2008;14:641-650.

8. Naing A, Hajjar J. Immunotherapy. Singapur: Springer 2017.

9. Carretero F. Loss of HLA class I in Prostate Cancer and restoration using adenoviral and adeno-associated viral vectors. Universidad de Granada 2017.

10. Maleno I, López-Nevot M, Cabrera T, Salinero J, Garrido F. Multiple mechanisms generate HLA class I altered phenotypes in laryngeal carcinomas: high frequency of HLA haplotype loss associated with loss of heterozygosity in chromosome region 6p21. Cancer Immunology, Immunotherapy 2002;51:389-396.

11. Maleno I, Cabrera C, Cabrera T, Paco L, López-Nevot M, Collado A et al. Distribution of HLA class I altered phenotypes in colorectal carcinomas: high frequency of HLA haplotype loss associated with loss of heterozygosity in chromosome region 6p21. Immunogenetics 2004;56.

12. Rodriguez T, Méndez R, Roberts C, Ruiz-Cabello F, Dodi I, Nevot M et al. High frequency of homozygosity of the HLA region in melanoma cell lines reveals a pattern compatible with extensive loss of heterozygosity. Cancer Immunology, Immunotherapy 2004;54:141-148.

13. Ryschich E, Cebotari O, Fabian O, Autschbach F, Kleeff J, Friess H et al. Loss of heterozygosity in the HLA class I region in human pancreatic cancer. Tissue Antigens 2004;64:696-702.

14. Drenou B, Tilanus M, Semana G, Alizadeh M, Birebent B, Grosset J et al. Loss of heterozygosity, a frequent but a non-exclusive mechanism responsible for HLA dysregulation in non-Hodgkin's lymphomas. British Journal of Haematology 2004;127:40-49.

15. Hiraki A et al. Loss of HLA Haplotype in Lung Cancer Cell Lines: Implications for

Immunosurveillance of Altered HLA Class I/II Phenotypes in Lung Cancer. Clinical Cancer Research 1999;5:933-936.

16. Bonifant C, Jackson H, Brentjens R, Curran K. Toxicity and management in CAR T-cell therapy. Molecular Therapy – Oncolytics 2016;3:16011.